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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/644,783	08/21/2003	Nancy C. Lan	1483.0370003	6918

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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	**PAPER NUMBER**
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	01/19/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 01/19/2007.

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Office Action Summary	Application No.	Applicant(s)	
	10/644,783	LAN, NANCY C.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/25/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 17-52* is/are pending in the application.

4a) Of the above claim(s) *22-33 and 46-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-15,17-21,34-45 and 50-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Acknowledgement is made of applicant's Response filed October 25, 2006 in response to O.A. mailed July 25, 2006

2. By Amendment filed October 25, 2006, claim 16 has been cancelled and claims 10-15 and 52 have been amended. Claims 10-15 and 17-52 are currently pending in the application, but claims 22-33 and 46-49 were withdrawn from consideration as being drawn to the non-elected invention. Claims 10-15, 17-21, 34-45 and 50-52 are currently pending for prosecution on the merits of the instant application.

3. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on May 15, 2006 prompted the new ground(s) of rejection presented in this Office action.

WO 03/020273 cited in IDS filed May 15, 2006 discloses that there is no significant difference in the value of ED_{50} for the instant 4-(4'-fluorophenoxy)benzaldehyde semicarbazone alone and in combination with gabapentin, in a 1:1 ratio, and concludes that not all the sodium channel blockers, active in model of chronic pain are expected to have synergistic effect with gabapentin (see page 17, lines 10-25).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 10-15, 17-21, 34-45 and 50-52 are rejected under 35 USC 112, first paragraph, because the specification while being enabling for the treatment of neuropathic pain with 1.25 mg/kg of 4-(4'-fluorophenoxy)benzaldehyde semicarbazone and 25 mg/kg of gabapentin, does not reasonably provide enablement for "treating or ameliorating neuropathic pain…a sodium channel blocker and a second agent selected from the group consisting of gabapentin, pregabalin, salts thereof and combination thereof…". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: the nature of the invention; the state of the prior art; the relative skill of those in the art; the predictability or unpredictability of the art; the breadth of the claims; the amount of direction or guidance presented; the presence or absence of working examples; and the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The present inventions are drawn to a method of treating or ameliorating neuropathic pain comprising administering "sodium channel blocker" in combination with a second agent selected from the group consisting of gabapentin, pregabalin, salts thereof and combination thereof, in any given dosage amounts.

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmacy art is high. The specification does not provide any competent evidence or disclosed

tests that are highly predictive for the therapeutic utility of the instant compounds encompassed by the instant claims.

The specification provides study showing the coadministration of 1.25 mg/kg of 4-(4'-fluorophenoxy)benzaldehyde semicarbazone (Co 102862) and 25mg of gabapentin in the neuropathic rats model, and discloses that the combination shows a synergistic effect (Example 1). However, there is no demonstrated correlation that the tests and results apply to the entire scope of "sodium channel blocker" in combination the second agent, in any dosage amounts, embraced by the instant claims.

As discussed above, evidenced by the post-dated reference (WO 03/020273), not all of dosage range of combination of 4-(4'-fluorophenoxy)benzaldehyde semicarbazone and gabapentin provide the synergistic effects. Furthermore, not all the sodium channel blockers, active in model of chronic pain are capable of having synergistic effect with gabapentin.

Thus, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to practice the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "substantially" in claim 17 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for

ascertaining what is meant by "substantially simultaneously", and one of ordinary skill in the art would not be reasonably apprised of the scope of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 10-15, 17-21, 34-45 and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (WO 9847869) in view of Rosenberg et al. (The Clinical Journal of Pain, 13:251-255, 1997), and further in view of Bueno (US 6242488) and Caruso et al. (US 6187338).

The claims read on use of a pharmaceutical composition comprising a sodium channel - blocker such as 4-(4'-fluorophenoxy)benzaldehyde semicarbazone in combination with gabapentin for the treatment, prevention or amelioration of chronic pain, more specifically "trigeminal neuralgia", "diabetic neuropathy" and "cancer pain". Further limitation includes the

administration of said drug(s) in "simultaneously" or "separately" (claim 17 or 18 respectively); "said first agent and said second agent are administered as part of a single pharmaceutical preparation (claim 19); various delivery dosage forms including oral (claims 21 and 40), parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal or buccal forms (claims 50 and 51).

Wang teaches the use of 4-(4'-fluorophenoxy)benzaldehyde semicarbazone for ameliorating chronic pain, neuropathic pain such as trigeminal neurologia or diabetic neuropathy (abstract; page 1 line 15 thru page 2, line 22; page 3, lines 27-28; page 4, line 4; page 25, lines 13-14; claims 1, 5, 7-8), wherein said compound is administered in the dosage range of 0.0025 to 50mg/kg orally or about 0.25 to about 10mg/kg intravenously (page 28, lines 3-23); and wherein said compound is prepared in various pharmaceutical dosage forms including oral, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal and buccal forms (page 29, line 13-20). Wang also teaches the use of sodium channel blocker (e.g., carbamzepine and lamotrigine) for treating neuropathic pain due to trigeminal neurologia and diabetic neuropathy (page 2, lines 5-22).

Rosenberg teaches the use of GABA analogs such as gabapentin for the treatment of chronic pain such as neuropathic pain (e.g., postherpetic neuralgia, diabetic neuropathy), wherein median dose of 600-2400mg, orally, is administered for the treatment of neuropathic pain (abstract; Table 1; results).

Bueno is being supplied as a supplemental reference to demonstrate the routine knowledge in preparing gabapentin in various dosage forms including oral, parenteral and intravenous administration (column 3, line 66 thru column 4, line 5).

Caruso is being supplied as a supplemental reference to demonstrate the routine knowledge in art in determining the delivery of various neuropathic pain-alleviating active ingredients including gabapentin in combination by separate administration or coadministration in single dosage forms (column 2, line 36; column 5, lines 8-14).

The teaching of Wang differs from the claimed invention (i) mainly in the combination use of sodium channel blocker such as 4-(4'-fluorophenoxy) benzaldehyde semicarbazone and gabapentin in treating chronic pain, namely "trigeminal pain", "diabetic neuropathy" and "cancer pain"; (ii) the specific dosage amounts of each active ingredients, and (iii) the delivery of said combination in various dosage forms including oral, parenteral, intravenous, inmuscular, intraperitoneal, transderal or bucal forms and the specific order of delivery of said combination.

With respect to the combination of sodium channel blocker such as 4-(4'-fluorophenoxy) benzaldehyde semicarbazone and gabapentin for the treatment of chronic pain,

To incorporate such teaching into the teaching of Wang, would have been obvious in view of Rosenberg who teaches the use of gabapentin for treating chronic pain such as neuropathic pain (e.g., neuralgia, diabetic neuropathy).

The above references in combination make clear that the sodium channel blocker (i.e., 4-(4'-fluorophenoxy)benzaldehyde semicarbazone) and gabapentin have been individually used for the treatment of chronic pain such as neuropathic pain. It is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The

combination of active ingredient with the same character is merely the additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).*

One having ordinary skill in the art would have been motivated to modify the teaching of Rosenberg such that the pharmacological activity of gabapentin would be enhanced by the addition of sodium channel blocker such as 4-(4'-fluorophenoxy)benzaldehyde semicarbazone while toxicity associated with high dose of gabapentin would be minimized by the combination of said sodium channel blocker. One having ordinary skill in the art would have expected that the claimed combination would be useful in treating chronic pain due to trigeminal neuralgia and diabetic neuropathy in view of combination of Wang and Rosenberg.

With respect to the optimization of dosage amounts of each ingredients, dosage forms and concurrent administration regimen,

Those of ordinary skill in the art would have been readily determined the optimum dosage amounts or drug delivery forms (e.g., oral, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal or buccal) or the order of administration (e.g., simultaneously, separately) by good medical practice and the clinical condition of the individual patient. One having ordinary skill in the art would have been motivated to determine optimum amounts of known active ingredients to maximize the efficacy of drugs while minimizing the adverse effects of the drugs. Determination of the appropriate dosage forms or frequency regimen for treatment involving each of the above mentioned formulations would have been routinely made by those of ordinary skill in the art and is within the ability of tasks routinely

performed by them without undue experimentation, especially in light of known therapeutic dosage amounts of each active ingredients and available dosage forms of said drugs in the art.

One having ordinary skilled in the art would have been motivated to make such modification to extend the usage of the claimed composition to accommodate patient's preference and needs where the compliance could be improved with effective and well tolerated drug. As discussed in preceding comments, such determination of optimal ranges of effective amounts of each component, dosage forms and concurrent administration regimen is well considered within the skill of the artisan, absent evidence to the contrary.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Response to Arguments

7. Applicant's arguments filed October 25, 2006 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that the phrase "substantially simultaneously" is definite in light of the specification ("the sodium channel blocker, gabapentin and/or pregabalin are administered in sequence or at the same time so long as effective blood levels of the sodium channel blockers, gabapentin and pregabalin are achieved at the same time".

This argument is not found persuasive. Although the specific embodiments are shown in the specification, it is considered that the meaning of the claims should be clear from the wording of the claim alone. Thus, the examiner maintains this rejection.

Applicant's argument in the response takes the position that the unexpected results shown in the specification (Example 1, page 32, line 24 through 33, line 2, and Figure 1) are not taught or suggested in the cited references, alone or in combination. The applicant asserts that the tactile anti-allodynia effect of 4-(4'-fluorophenoxy) benzaldehyde semicarbazone and gabapentin combination is not merely additive of the two individual components, but rather is synergistic or superior unexpected results (greater than the sum of the individual compounds' effect) over the prior art.

This argument is not found persuasive. As discussed above, evidenced by the post-dated reference (WO 03/020273), not all of dosage range of combination of 4-(4'-fluorophenoxy) benzaldehyde semicarbazone and gabapentin provide the synergistic effects. Since the scope of the instant invention includes the dosage ranges having the additive effect, the cited references in combination make obvious the instant invention.

Conclusion

8. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on May 15, 2006 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. No Claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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